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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/954,972	09/17/2001	George Jackowski	2132.074	7710

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EXAMINER

NGUYEN, BAO THUY L

ART UNIT PAPER NUMBER

1641

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/954,972

Applicant(s)

JACKOWSKI ET AL.

Examiner

Bao-Thuy L. Nguyen

Art Unit

1641

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 23 April 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 13 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 13 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Election/Restrictions***

1. Applicant's election without traverse of Group V, claim 13 in Paper dated 4/23/2004 is acknowledged.
2. Claims 1-12 and 14-20 have been cancelled.

### ***Specification***

3. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

The specification does not specifically teach the detection of anti-GFAP using IgG. The specification teaches the use of SELDI-TOF-MS to elucidate GFAP, and teaches, in general, immunoassays for detecting analytes such as antigens and antibodies. However, the specification fails to teach the detection of anti-GFAP using IgG.

### ***Claim Rejections - 35 USC § 112, second paragraph***

4. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 is indefinite because it lacks a correlation between the detection of GFAP antibodies and fragments thereof and the diagnosis of prediabetes.

The recitation of "a diagnostically effective amount" is unclear since this amount has not been defined. Therefore, the boundaries of the claim are not discernible.

The recitation of “prediabetes” is confusing since “prediabetes” is not a disorder per se.

The claim is also confusing since it is unclear if it is a method of diagnosing type 1 diabetes, or if it is a method of screening for prediabetes. The recitation of “anti-GFAP IgG useful as a predictive marker of Type 1 diabetes” does not allow the metes and bounds of the claim to be ascertained. According to the claim, if autoantibodies to GFAP are useful as a predictive marker of Type 1 diabetes, will their detection or presence be indicative of prediabetes, regardless of clinical form, i.e. Type 1 or Type 2.

*Claim Rejections - 35 USC § 112, first paragraph*

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is directed to a method for prediabetes screening by detecting autoantibodies to Glial Fibrillary Acidic Protein (GFAP). Such a method is not enabled by the specification as originally filed.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the

state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The specification states that diabetes-associated autoimmunity in NOD mice and humans targets a closely similar set of autoantigens, and presents SELDI-TOF-MS evidence that GFAP autoantibodies were detected in NOD mice, diabetic patients and relatives with probable prediabetes, as well as evidence from healthy controls. From this evidence, the specification concludes that autoimmunity against peri-insular SC is characteristic of human and NOD mouse Type 1 diabetes (pages 12-13).

The specification fails to teach one skilled in the art whether autoantibodies to GFAP are positively correlated with prediabetes or with diabetes. The evidence presented is not convincing because it fails to take into consideration the required criteria for a diagnostic assay.

According to Strongin (1993, "Sensitivity, Specificity, and Predictive Value of Diagnostic Tests: Definitions and Clinical Applications", in *Laboratory Diagnosis of Viral Infections*, Lennette, e., ed., Marcel Dekker, Inc., New York, pp. 211-219) a number of characteristics need to be considered in the development of any suitable diagnostic assay. These characteristics include the following: (1) the sensitivity of the assay; (2) the true-positive test rate; (3) the false-negative test rate; (4) the specificity, or percentage of patients without the disease who will display a negative results; (5) the true-negative test rate; (6) the false-positive test rate; (7) the predictive value, or the probability that the test result is correctly indicating the presence or absence of the disease; (8) the prevalence, or number of patients in any given population that have the disease in question; (9) the efficiency or percentage of all results that are true; (10) the

accuracy of the recited diagnostic assay. Additional considerations must also be examined to enable the clinician to practice the invention including assessment of the following: (1) when is the maximum sensitivity desired?; (2) when is the maximum specificity desired?; (3) when is the maximum efficiency desired?; (4) How is the maximum sensitivity or specificity achieved?; (5) how is the predictive value maximized? An essential understanding of these factors is required to enable the skilled artisan to accurately use and interpret any given diagnostic test. Since the specification lacks any teaching of how the diagnostic tests were performed, or any information regarding the patients from which the samples were taken, and whether any considerations were given to any of the characteristics state above, it would require undue experimentation for one skilled in the art to make and use the invention as claimed.

According to these teachings, the specification lacks proper guidance to enable one skill in the art to determine the incidence of disease as related to the presence or absence of GFAP, for example. The specification does not teach any of the above criteria, nor does it disclose how test results should be interpreted and related to a prediabetic condition. The specification discloses that using SELDI-TOF-MS, GFAP is found in both diabetic patients and in relatives exhibiting signs of autoimmunity (i.e. prediabetes), therefore, it does not appear that by detecting the presence of GFAP, one is able to positively diagnose Type I diabetes.

Likewise, the prior art of record is silent on any correlation between autoantibodies to GFAP and diabetes or prediabetes. Furthermore, the art of record teaches away from extrapolating data in NOD mice to human. For example, Atkinson (*Nature Medicine*. Vol. 5, No. 6, 1999) teaches that NOD mice cannot always be relied upon for extrapolation to human.

Specifically, Atkinson discloses that even though the understanding of the pathogenic mechanisms underlying type 1 diabetes development in NOD mice is quite advanced, genus-specific differences between the NOD mice and human that restrict their interpretation are unavoidable. Specifically, Atkinson teaches that the etiology for type 1 diabetes is both complex and multifactorial. One example involves the destruction of  $\beta$  cells which entails both necrotic and apoptotic events in response to invasion of the islets by leukocytes. In NOD mice, there are large numbers of leukocytes in the insulitic infiltrates of NOD mice suggesting lymph node formation around islets. In human, however, insulinitis acute-onset diabetic is very different from the in NOD islets. Therefore, the teaching that because GFAP is found in both NOD mice and human, it is evidence for prediabetes is not convincing for two reasons: (1) GFAP has not been definitely proven to be diagnostic of prediabetes in NOD mice, and (2) data from NOD mice cannot always be extrapolated to human.

Because of the lack of description in the specification for the claimed method, it cannot be conclusively determined from the data presented in Figures 1-4 that anyone or everyone who has these autoantibodies suffers from diabetes or prediabetes. Therefore, it is maintained that one of ordinary skill in the art could not make and use the invention as claimed without undue experimentation.

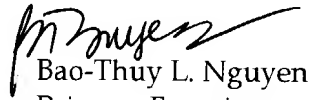
### *Conclusion*

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao-Thuy L. Nguyen whose telephone number is (571) 272-0824. The examiner can normally be reached on Tuesday and Thursday from 9:00 a.m. - 4:30 p.m..

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
Bao-Thuy L. Nguyen  
Primary Examiner  
Art Unit 1641